



NASA SPACE RADIATION PROGRAM

Biological-Based Risk Assessment for Space Exploration - What's New?

Francis A. Cucinotta

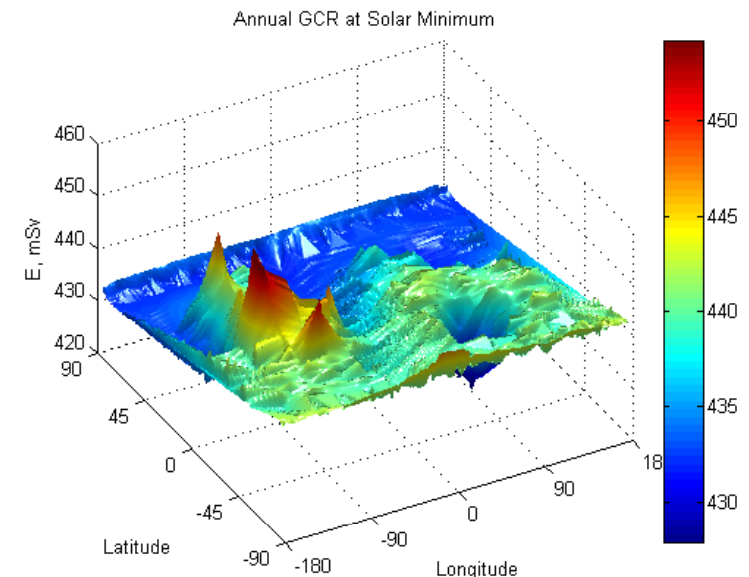
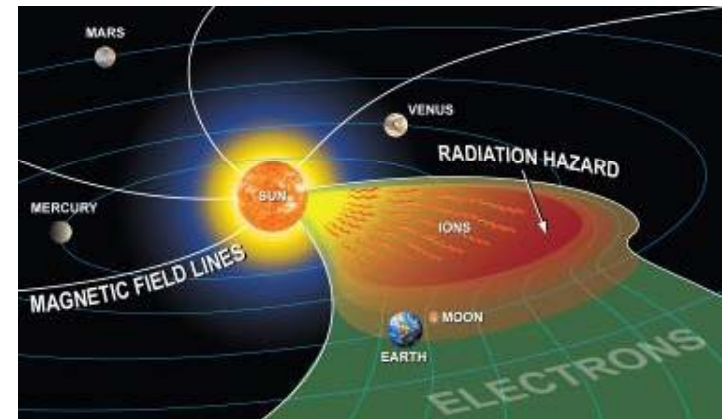
NASA, Lyndon B. Johnson Space Center

**International Symposium for Radiation Research
and Medical Physics, May 31 2011**

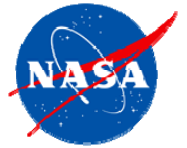


Estimating Space Radiation Space to Astronauts

- NASA is developing new approaches to radiation risk assessment:
 - Probabilistic risk assessment framework
 - Tissue specific estimates
- Research focus is on uncertainty reduction
 - Smaller tolerances are needed as risk increases, with <50% uncertainty required for Mars mission
- NASA 2010 Model
 - Updates to Low LET Risk coefficients
 - Risks for Never-Smokers
 - Track Structure and Fluence based approach to radiation quality
- Pathway to NASA 2020 Model
 - NASA Space Radiation Lab (NSRL) experimental program
 - Modular Systems Radiation Biology

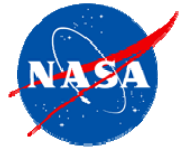


GCR doses on Mars

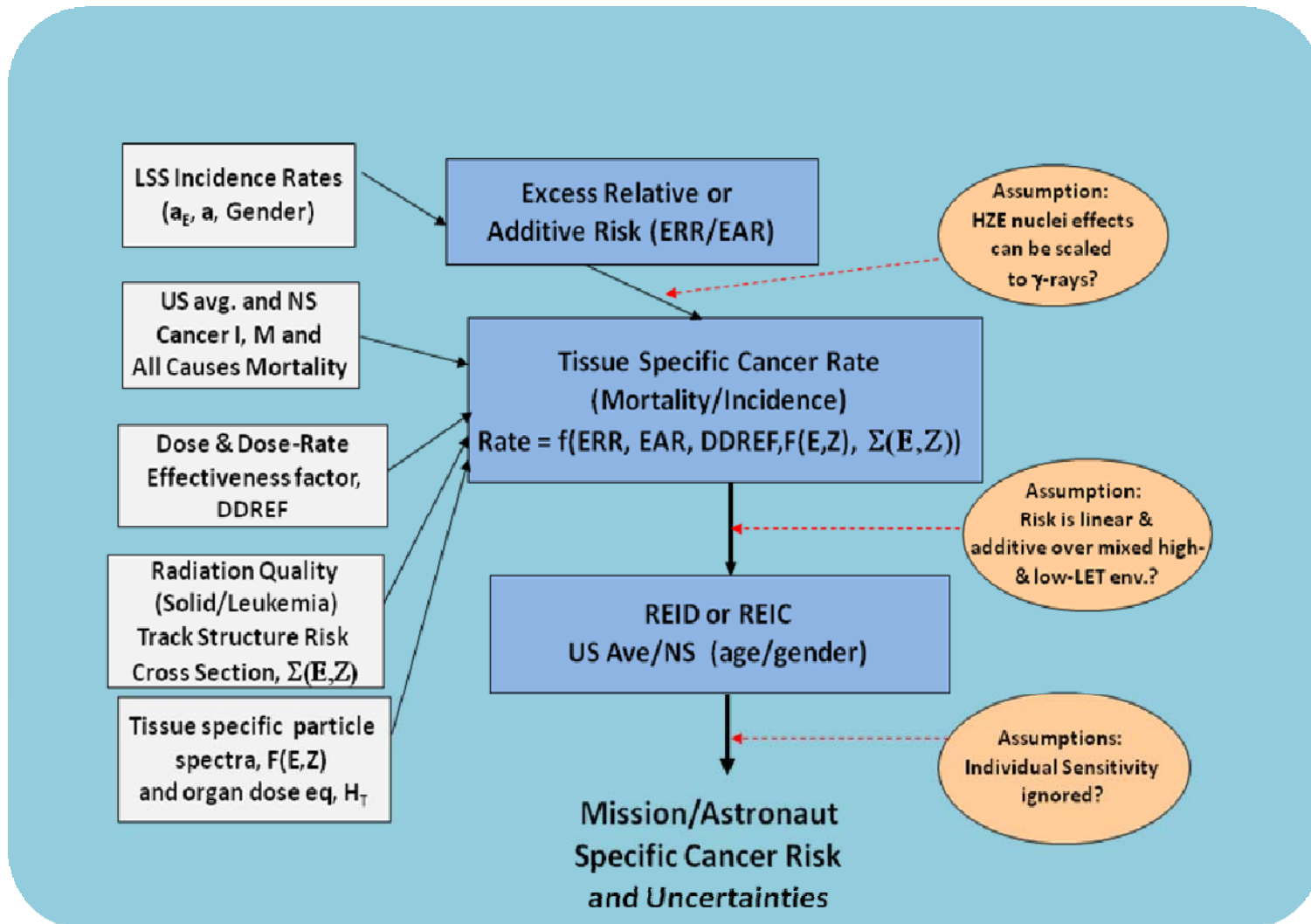


NASA 2010 Cancer Projection Model

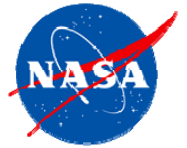
- NASA uses NCRP Report 132, published in 2000, for radiation protection estimates and setting dose limits for astronauts
 - Based on DS86, Japanese Life-span Study (LSS) data from 1993, and mortality risk transfer model
- Recent analysis of Low LET Risk Coefficients were made by UNSCEAR, BEIR VII, and Preston et al. (2007)
 - DS02 Dose estimates and longer follow-up times of LSS
- NASA comparison of recent approaches for Space Station and Exploration planning requirements:
 - Incidence based Risk Transfer is preferred model (BEIR VII)
 - UNSCEAR tissue specific incidence models for risk coefficients
 - Risks for Never-smokers such as Astronauts considered
 - Reduces lung, esophagus, stomach and bladder cancer risks compared to Ave. U.S. Model
 - Larger reduction if Multiplicative risk transfer is used



Standard Model for Cancer Risk Estimates: Basis for NASA 2010 Estimates



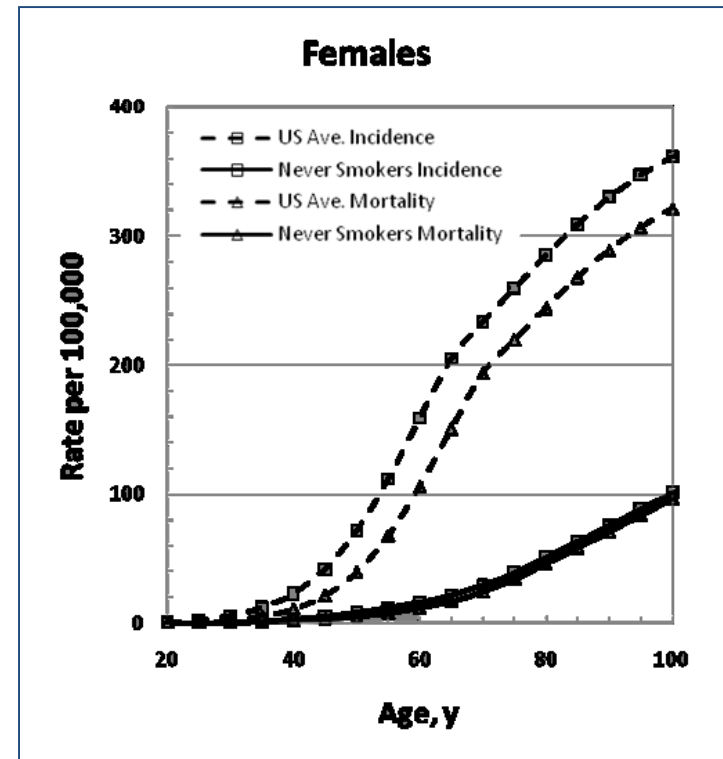
LSS = Japanese Lifespan Study; NS = Never-smoker



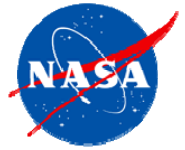
Radiation Risks for Never-Smokers

- More than 90% of Astronauts are never-smokers and remainder are former smokers
- Smoking effects on Risk projections:
 - Epidemiology data confounded by possible radiation-smoking interactions, and errors documenting tobacco use
 - Average U.S. Population used by NCRP Reports 98 and 132
- NASA Model projects a 20 to 40-% risk reduction for never-smokers compared to U.S. Ave.
 - Larger decreases are possible if more were known on Risk Transfer models
 - Balance between Small Cell and Non-Small Cell Lung Cancer a critical question including high LET effects

Lung cancer in Unexposed

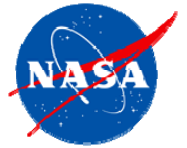


Thun et al., PLoS Med (2008)



CDC Estimates of Smoking Attributable Cancers

Relative Risk to Never-smokers (NS)				RR for NS to U.S. Avg
Males	Current smokers	Former smokers	Never-smokers	RR(NS/U.S.)
Esophagus	6.76	4.46	1	0.27
Stomach	1.96	1.47	1	0.71
Bladder	3.27	2.09	1	0.50
Oral Cavity	10.89	3.4	1	0.23
Lung*	23.26	8.7	1	0.11
Females	Current smokers	Former smokers	Never-smokers	RR(NS/U.S.)
Esophagus	7.75	2.79	1	0.35
Stomach	1.36	1.32	1	0.85
Bladder	2.22	1.89	1	0.65
Oral Cavity	5.08	2.29	1	0.46
Lung*	12.69	4.53	1	0.23

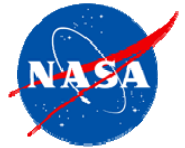


Risk Transfer Models

- ERR and EAR models are fitted to Epidemiology data
 - Leukemia and overall solid cancer mortality
 - Tissue specific for Incidence models
- NCRP 132: Mortality transfer to Ave. U.S. Pop. as mean of Multiplicative and Additive Transfer ($v_T=0.5$) for solid cancer, and Additive transfer for Leukemia
- BEIR VII recommends Incidence transfer with conversion to mortality using ave. U.S. incidence & mortality rates (λ_0)

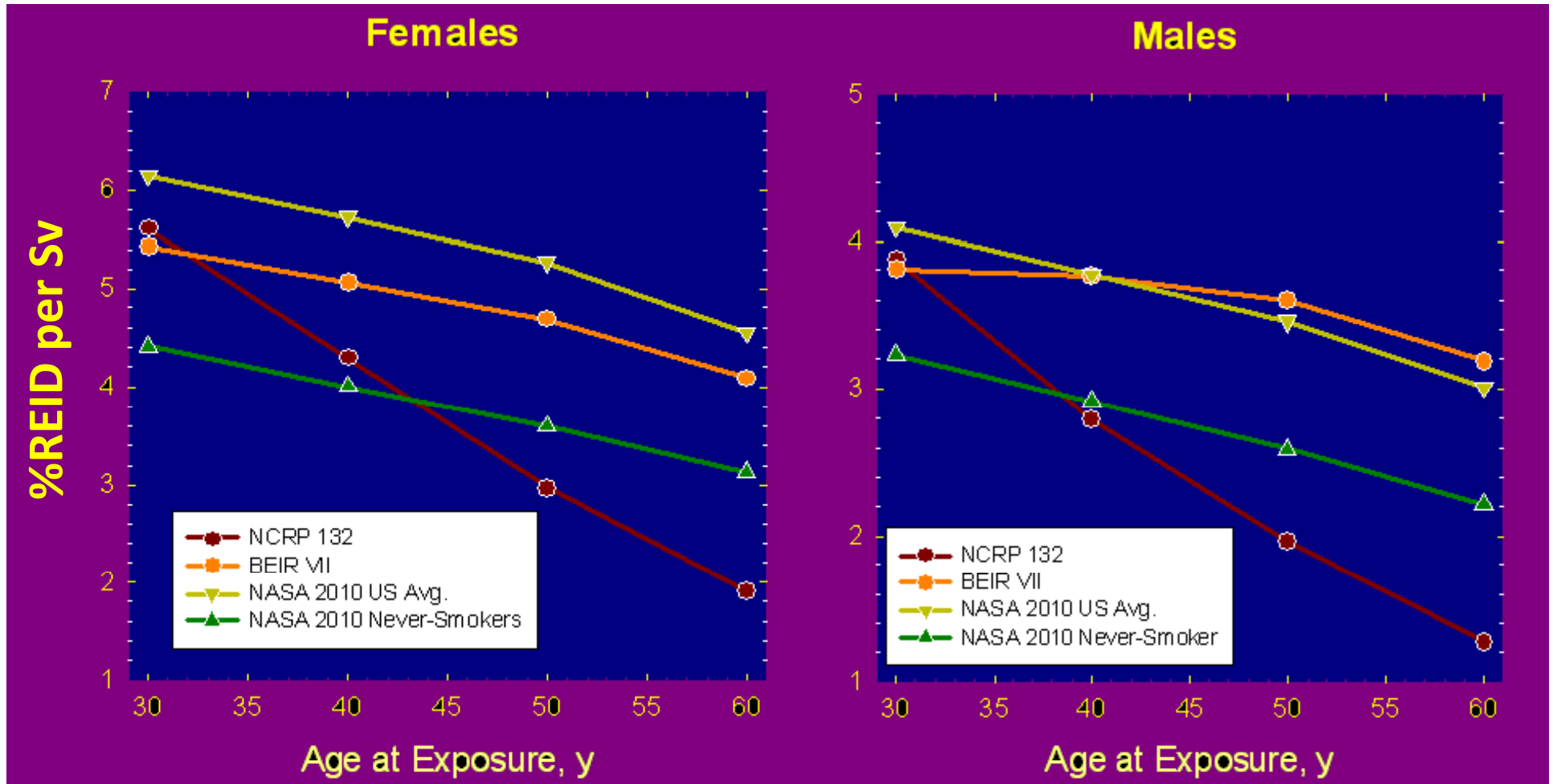
$$\lambda_M(H_T, a_E, a) = [v_T ERR(a_E, a) \lambda_{0M}(a) + (1 - v_T) \frac{\lambda_{0M}(a)}{\lambda_{0I}(a)} EAR(a_E, a)] \frac{H_T}{DDREF}$$

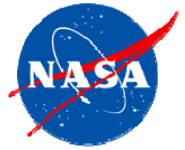
- Incidence rates are more stable over time
- Tissue specific projections vital for SPE's where larger organ to organ dose variations occur and for Attributable risk calculations
- LSS Incidence transfer model reduces age at exposure dependence of risk estimates compared to LSS mortality transfer model
 - Tissue specific models needed for SPE's and Attributable risk
 - Age was NASA's leading "trade variable"



Point Estimates: Risk of Exposure Induced Death (REID)

Age at Exposure NASA's Leading Trade Variable?

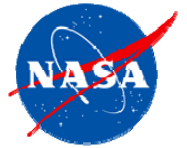




Fatal lung cancer risks per Sv (DDREF=2)

Transfer model impact much larger change than >100 cm of GCR shielding– the 100 Billion Dollar question?

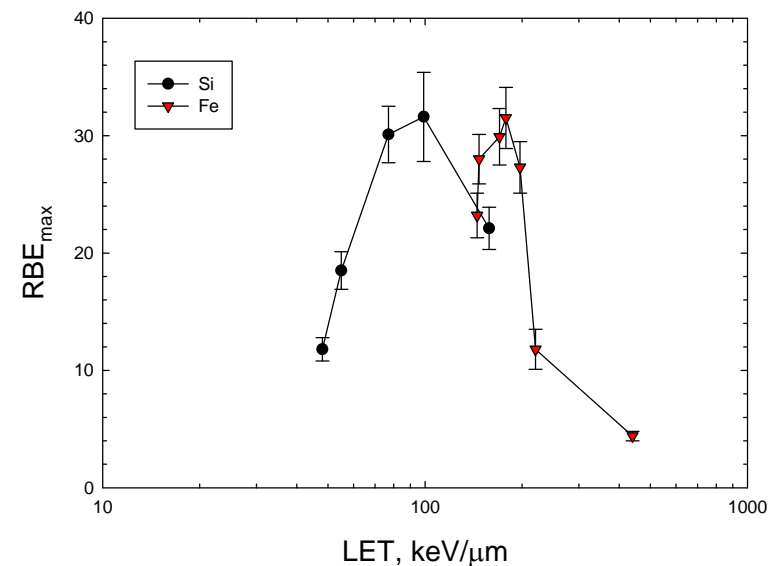
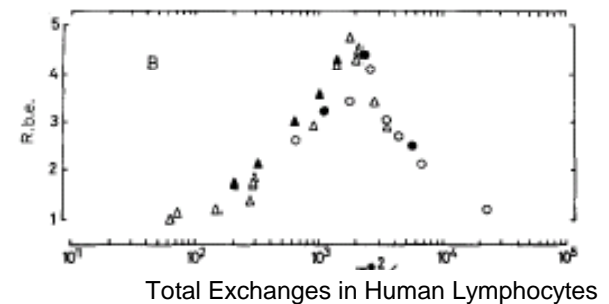
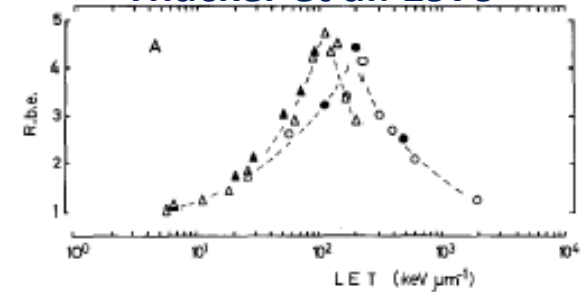
		% REID, Females			% REID, Males		
Age at Exposure		35, y	45, y	55, y	35, y	45, y	55, y
Model Type	Model rates	Average U.S. Population, 2005					
Additive	BEIR VII	1.20	1.20	1.18	0.65	0.66	0.66
	UNSCEAR	1.28	1.27	1.22	0.71	0.71	0.69
	RERF	1.33	1.34	1.32	0.72	0.73	0.73
Multiplicative	BEIR VII	2.88	2.74	2.38	0.95	0.92	0.83
	UNSCEAR	3.56	3.50	3.23	1.17	1.17	1.11
	RERF	3.71	4.16	4.21	1.13	1.30	1.37
Mixture	BEIR VII	2.04	1.97	2.78	0.80	0.79	0.74
	UNSCEAR	2.43	2.39	2.23	0.94	0.94	0.89
	RERF	2.53	2.77	2.78	0.92	1.02	1.05
Never-smokers							
Multiplicative	BEIR VII	0.44	0.41	0.37	0.15	0.15	0.14
	UNSCEAR	0.57	0.57	0.54	0.15	0.15	0.14
	RERF	0.55	0.61	0.66	0.14	0.15	0.16
Mixture	BEIR VII	0.85	0.84	0.81	0.40	0.40	0.38
	UNSCEAR	0.96	0.95	0.91	0.46	0.45	0.42
	RERF	0.98	1.01	1.02	0.46	0.47	0.45
Generalized Multiplicative	RERF, Generalized	0.39	0.47	0.53	0.16	0.17	0.20
	Multiplicative for never-smokers						

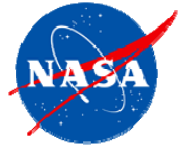


NASA Radiation Quality Description

- ICRP W_R or $Q(L)$ inadequate for Space radiation, and is Not informed by existing radiobiology results:
 - Leukemia lower RBE than solid cancers
 - Energy at peak RBE depends on Particle charge number not LET
 - Slope of rise and fall with LET inaccurate in ICRP $Q(L)$
 - RBE depends on charge Z and energy E , and not LET alone
- ICRP assume ion with higher Z has higher effectiveness than lower Z at fixed LET; not supported by track models or Expt.'s

Thacker et al. 1979

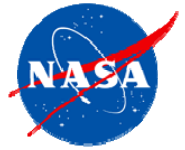




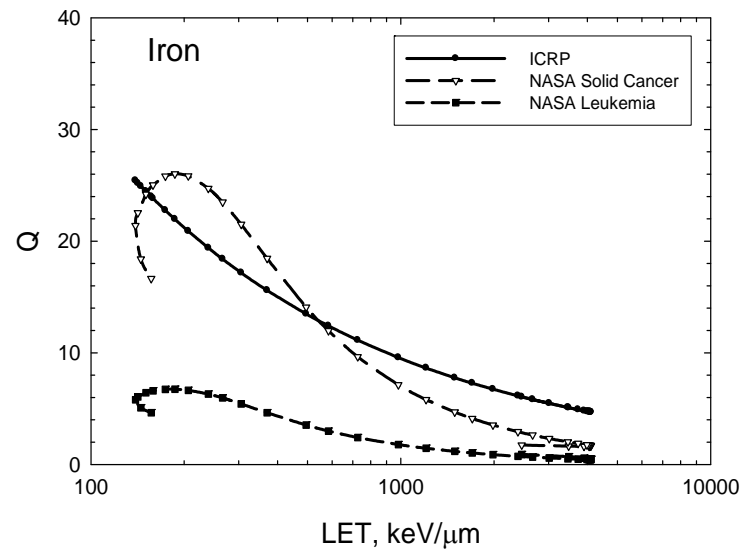
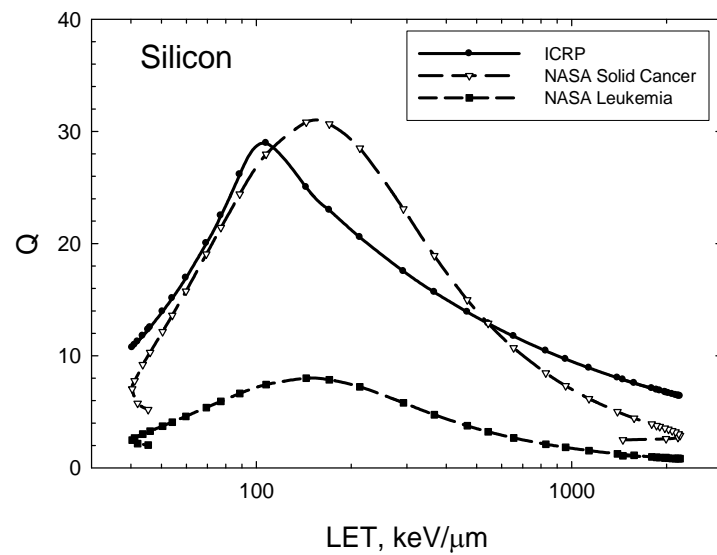
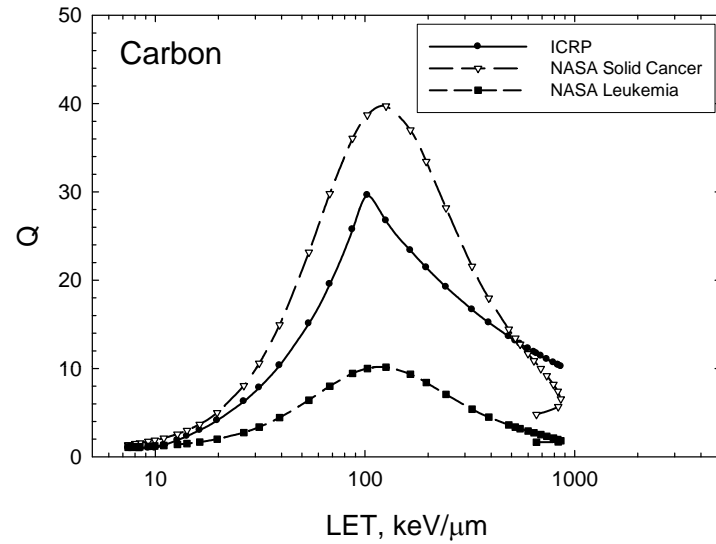
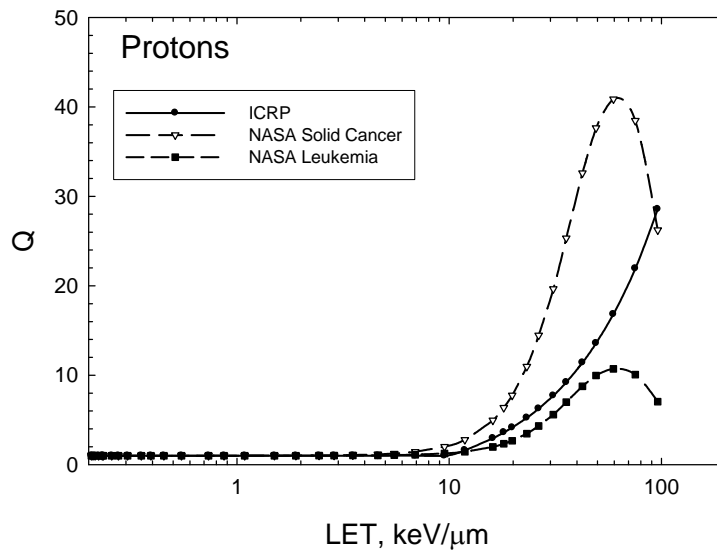
NASA Approach to Radiation Quality

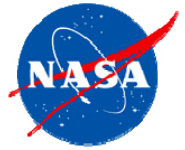
- Risk is calculated at tissue sites not using Radiation weighting factors
- Track structure and existing radiobiology data should be used to guide choice on functional forms
- Human data for Thorostrast (Boice et al.), AML data in mice, and human cell culture expt.: Leukemia RBE smaller than solid cancer RBE
- Maximum effectiveness per particle can be estimated by experiments for RBE_{\max}
- The maximum occurs at “saturation point” of cross section for any Z
- Delta-ray effects for relativistic particles should be accounted for in Q model
- Existing data shows (E,Z) or Z^2/β^2 better descriptors than LET; track structure models predict
- Well defined Probability distribution functions (PDF) to account for variation of possible parameter values (Σ_0 , m, and κ)

$$Q_{NASA} = (1 - P(E, Z)) + \frac{c \Sigma_0 P(E, Z)}{LET}; P = (1 - e^{-Z^2 / \beta^2 / \kappa})^m P_{TD}$$

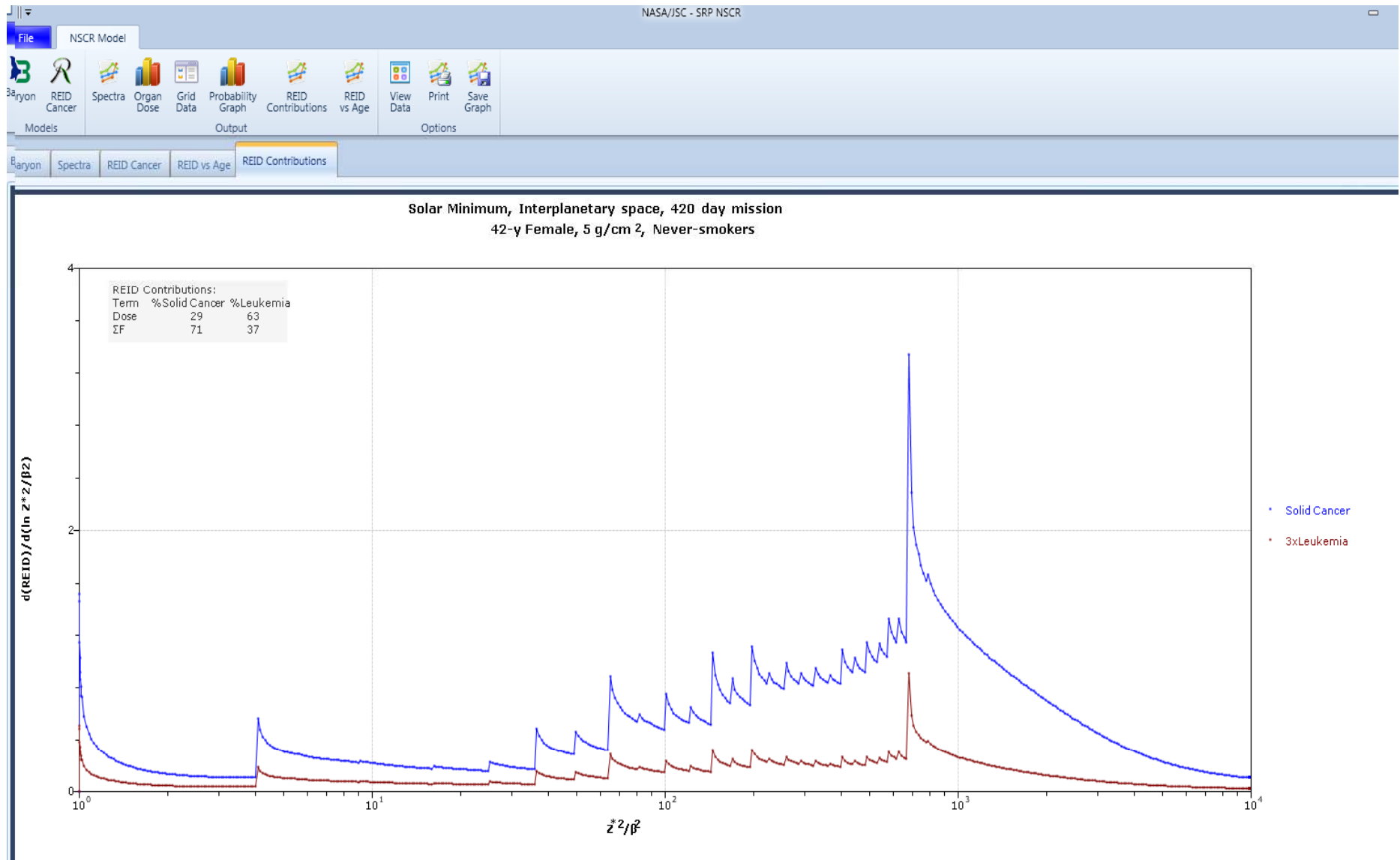


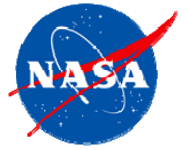
Comparison to ICRP Model





NASA Cancer Risk GUI

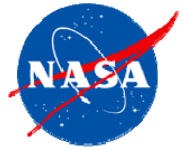




Low LET Uncertainties: Problems for Mars mission

- Published analysis shows about 2-fold uncertainty for 95% CL before Q and space physics uncertainties are considered
 - Statistical, dosimetry, transfer model and DDREF uncertainties
- NASA Goal of $\pm 50\%$ error for Mars mission never reached in “Standard Model” due to low LET uncertainties alone

Analysis	%Risk for 0.1 Sv	Comment
NCRP Report 126	0.37 [0.115, 0.808]	Gender avg. with 90% CI
BEIR VII Males	0.48 [0.24, 0.98]	95% CI
BEIR VII Female	0.74 [0.37, 1.5]	95% CI
UNSCEAR Solid Cancer	0.502 [0.28, 0.735]	Gender avg. with 90% CI, DDREF uncert. not considered
UNSCEAR Leukemia	0.061 [0.014, 0.118]	Gender avg. with 90% CI
NASA 2010	0.38 [0.139, 0.76]	40-y Female Never-smoker with 95% CI



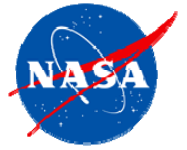
“Safe” days in Space: Uncertainties estimated using subjective PDFs propagated using Monte-Carlo techniques

%REID predictions and 95% CI for never-smokers and average U.S. population for 1-year in deep space at solar minimum with 20 g/cm² aluminum shielding:

a_E, y	%REID for Males and 95% CI			%REID for Females and 95% CI		
	Avg. U.S.	Never-Smokers	Decrease (%)	Avg. U.S.	Never-Smokers	Decrease (%)
30	2.26 [0.76, 8.11]	1.79 [0.60, 6.42]	21	3.58 [1.15, 12.9]	2.52 [0.81, 9.06]	30
40	2.10 [0.71, 7.33]	1.63 [0.55, 5.69]	22	3.23 [1.03, 11.5]	2.18 [0.70, 7.66]	33
50	1.93 [0.65, 6.75]	1.46 [0.49, 5.11]	24	2.89 [0.88, 10.2]	1.89 [0.60, 6.70]	34

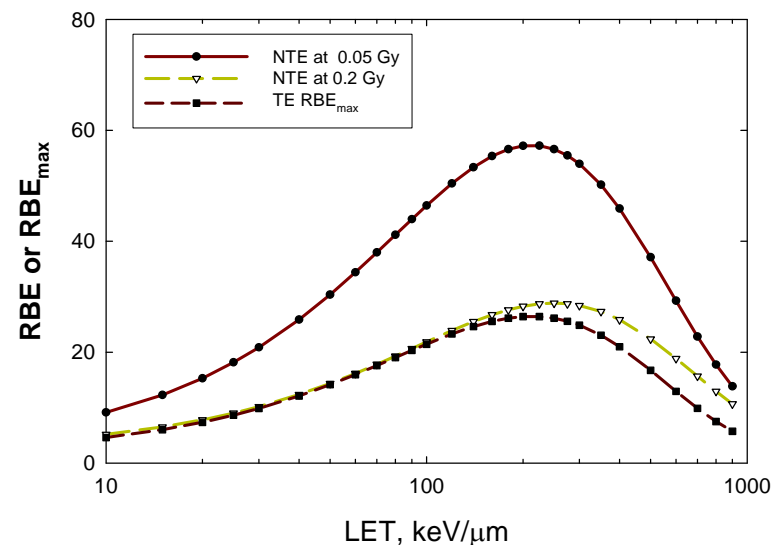
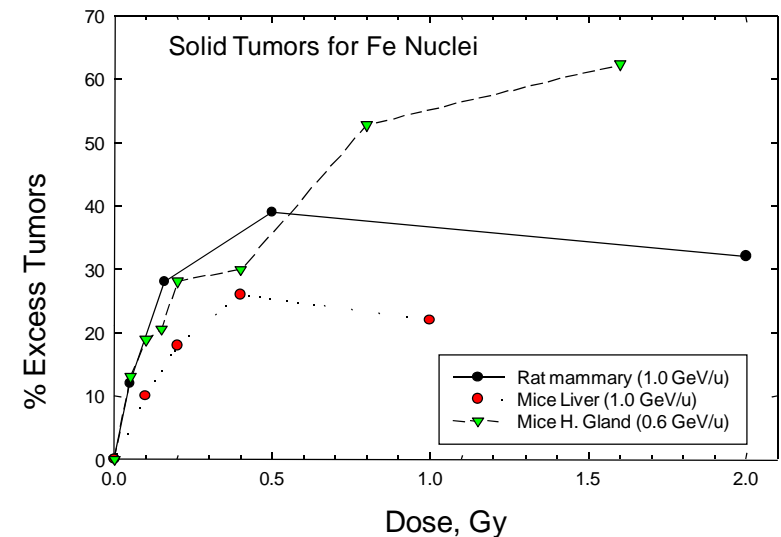
Maximum Days in Deep Space with 95% Confidence to be below Limits (alternative quality factor errors in parenthesis):

a_E, y	NASA 2005	NASA 2010 Avg. U.S.	NASA 2010 Never-Smokers
Males			
35	158	140 (186)	180 (239)
45	207	150 (200)	198 (263)
55	302	169 (218)	229 (297)
Females			
35	129	88 (120)	130 (172)
45	173	97 (129)	150 (196)
55	259	113 (149)	177 (231)

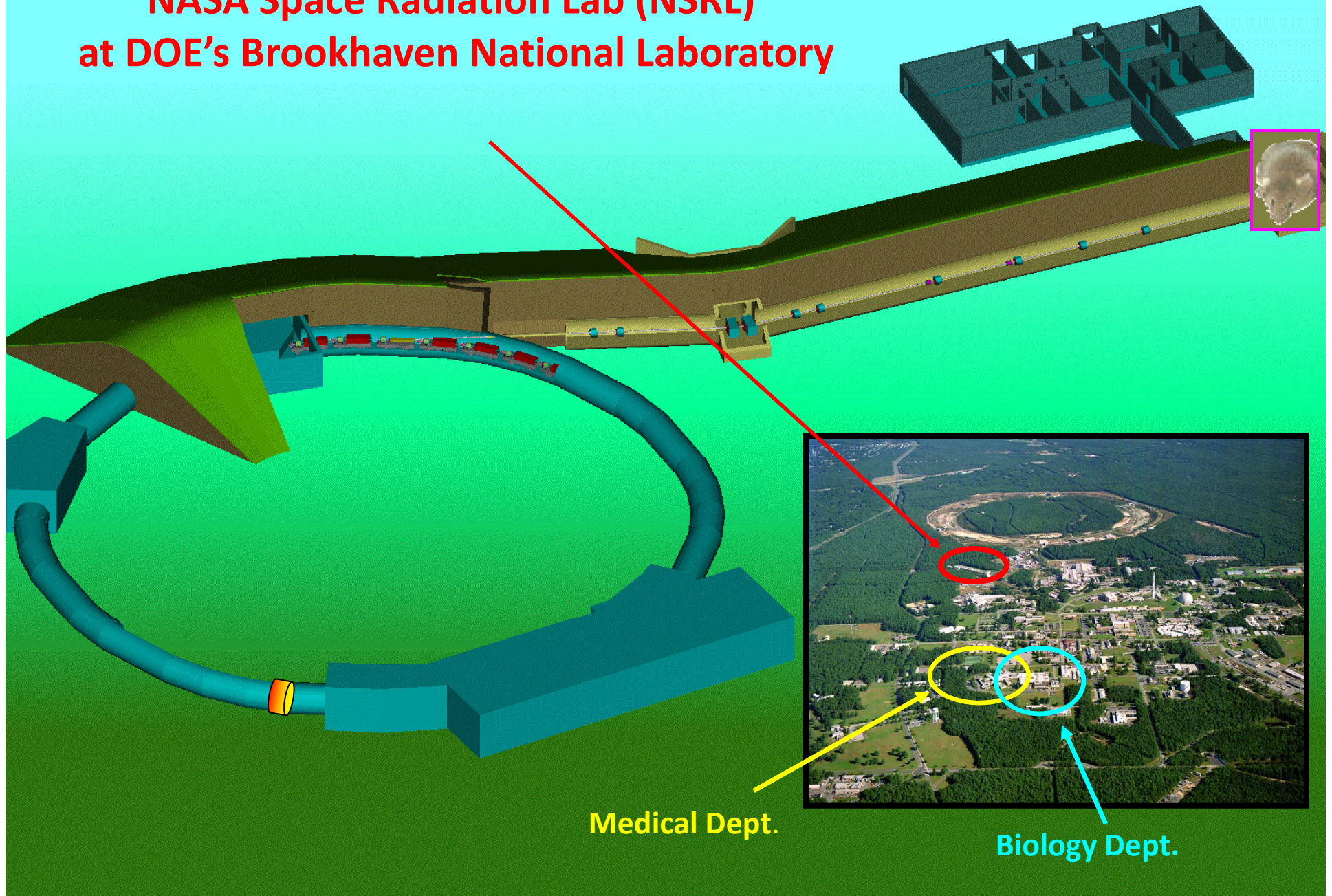


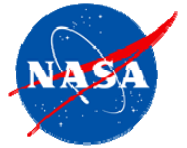
Uncertainties at Low Heavy ion Dose

- Heavy ion tumor dose response bends at low dose making estimates of RBE_{max} unreliable
- Alpen et al. and Edwards arbitrarily cut high dose data in H. Gland expt. to estimate RBE's of 20 to 40 for individual ions
- Cucinotta and Chappell (2010) modeled bending in response and made global fit to all data with alternative non-linear term at low dose to represent non-targeted effects.
 - **NTE model provides best fit to data**
- Heavy ion experiments related to cancer risk made at doses above 0.4 Gy are not very useful. Distinct mechanisms occur at low vs high dose (inflammation, immune response, NTE, oxidative stress, etc) and higher than exploration missions



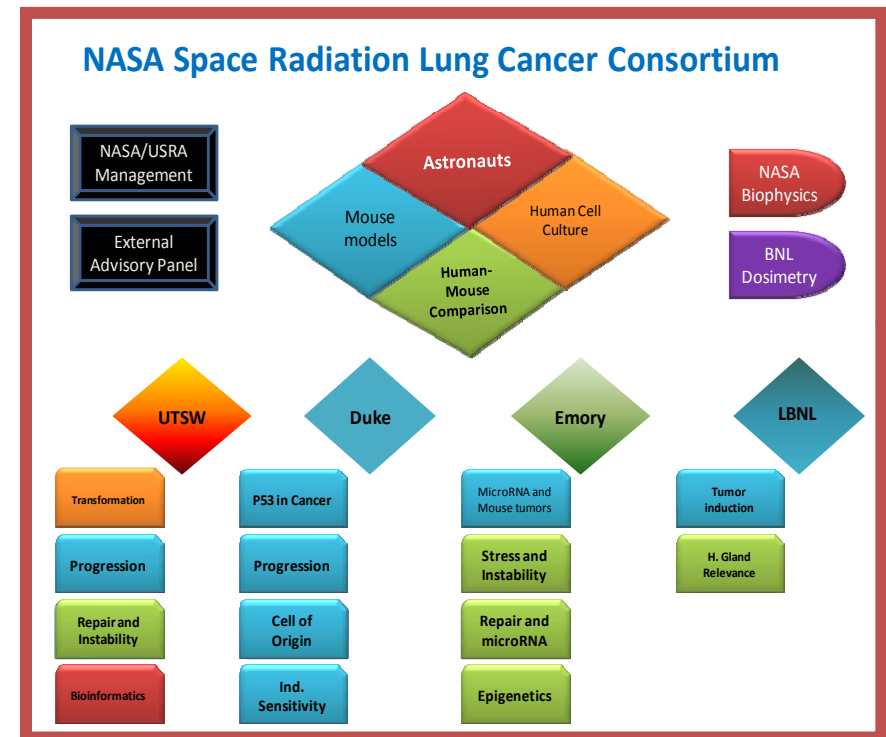
NASA Space Radiation Lab (NSRL) at DOE's Brookhaven National Laboratory

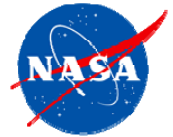




NASA Risk 2020- New Approaches are needed

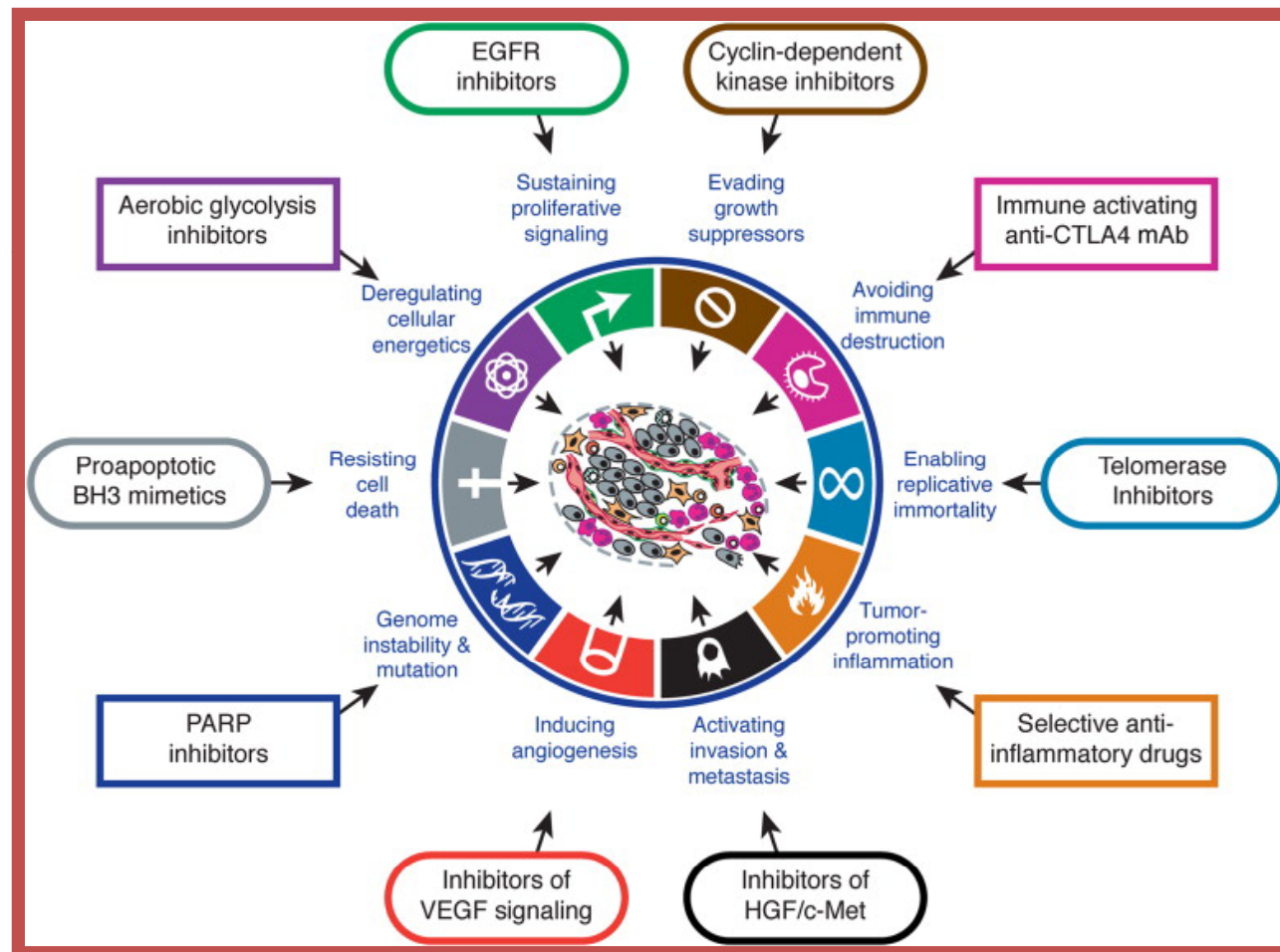
- Inherent uncertainties in “Standard” model points to the need for new approaches
- What would we do if there were no low LET human cancer data?
- Systems biology for disease modeling is most viable approach
- NASA has selected 5 NASA Specialized Centers of Research (NSCORs) and several related Grants using mouse models of colorectal, liver, leukemia, Harderian gland, and lung cancer from space radiation.
- The NASA Lung Consortium is a \$28 M effort to focus on risks of non-small lung cancer (NSCLC) and small-cell lung cancer (SCLC) from space radiation.
- CNS and Circulatory disease risks from space radiation are a major concern for space exploration with 12 Grants funded by NASA and the CNS NSCOR.





The Hallmarks of Cancer (2011):

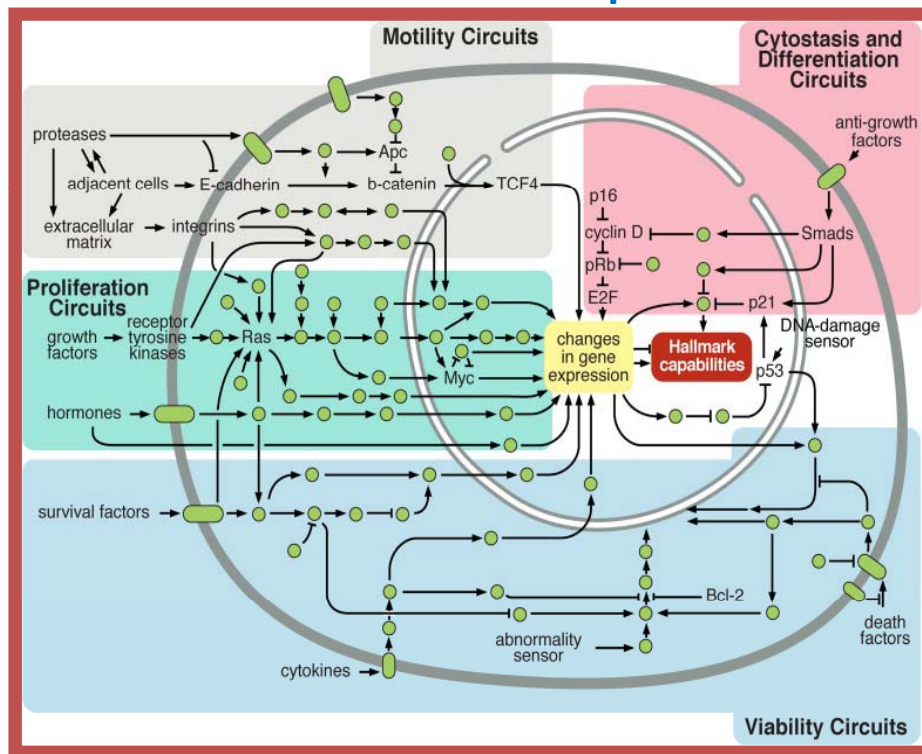
Recent focus of NASA R01 type grants is to study 2 or more Cancer Hallmarks using NSRL



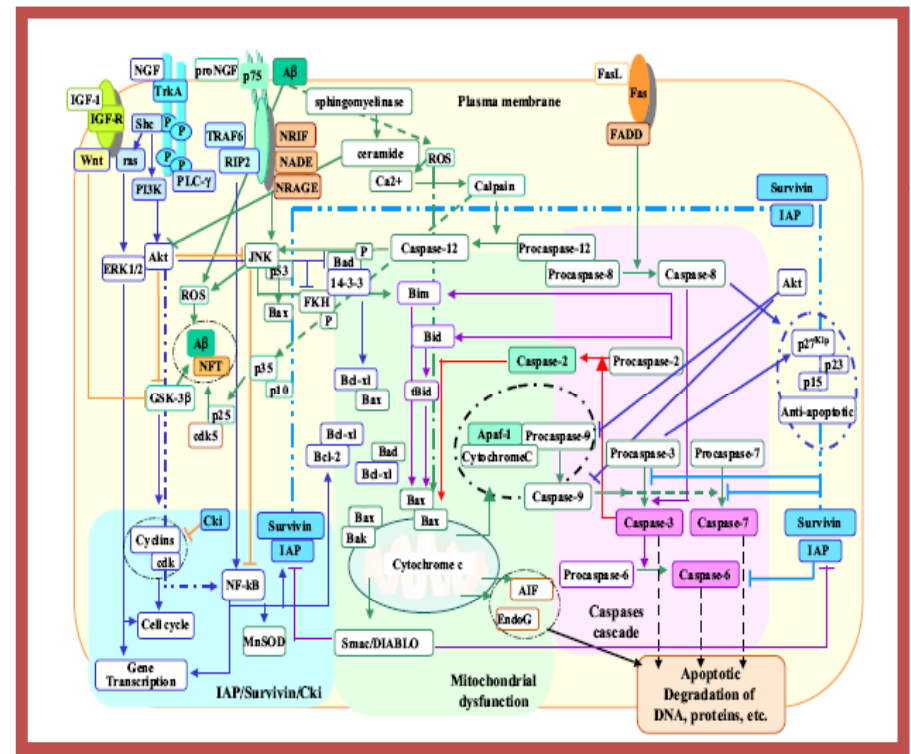


Modular Systems Biology: The complexity of biological systems suggests a Modular framework

Modules in Cancer Development

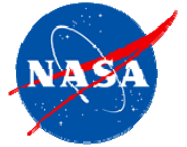


Modules in Neuronal Death



Hanahan & Weinberg, Cell (2011)

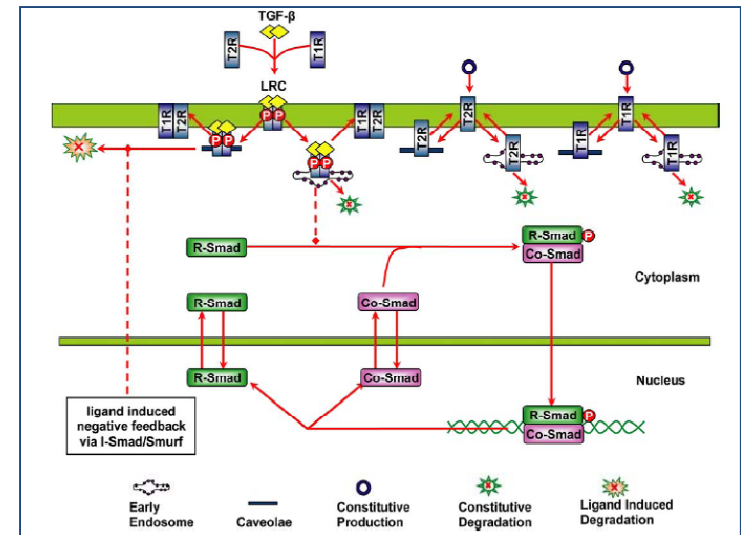
Alberghina & Colangelo, BMC Neuro. (2006)



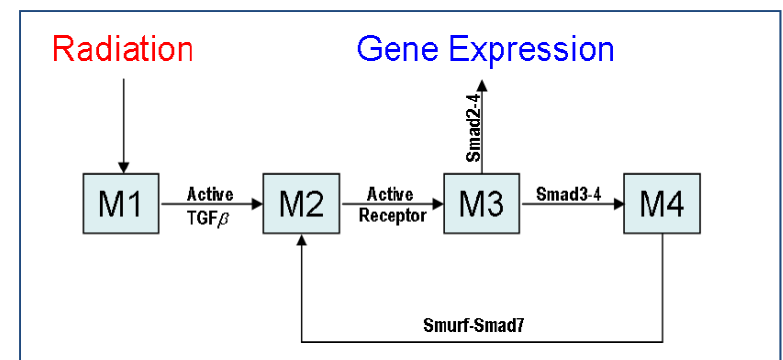
Modeling Approaches

- Track structure models are well developed & can be applied to define “substrates” to perturb modules important in cancer and degenerative risks.
 - Important work on defining tissue structures and DNA and non-DNA targets is needed
- Pathway modeling made on at least 3 levels
 - Molecular binding and interaction
 - Deterministic O.D.E.
 - Stochastic approaches such as Chemical Master Eq.; hybrid for fast and slow reactions
- Mathematical pathway modules have been created for most pathways of interest.
- Mathematics of Modular systems offers great simplicity to application
- Challenges include the many rate constants that appear (these are fundamental quantities) and to define the relationships between pathways, interacting modules to tissue function and disease

TGFbeta-Smad Pathway

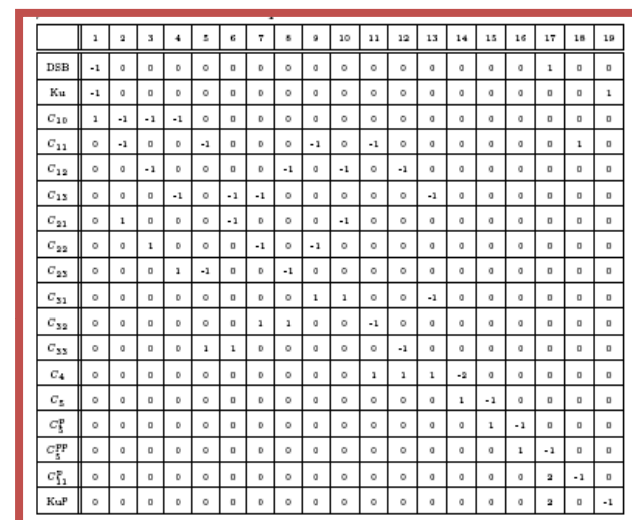


Modular Representation



Stability analysis applied to modules and interactions

Interactions suggested by experiments can be described theoretically using stability analysis to validate and predict (Li and Cucinotta, 2011)

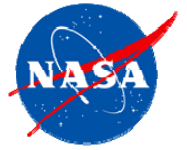


Sequential NHEJ Pathway

Two-Phase NHEJ Pathway

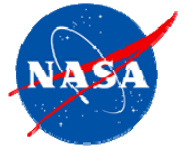
Figure 4: Short term dynamics of NHEJ proteins - Sequential Model vs Two-phase Model.

Figure 4: Short term dynamics of NHEJ proteins - Sequential Model vs Two-phase Model



Conclusions

- Never-smokers estimated at 20 to 40% less overall cancer risk compared to Ave. US population
- Much Larger (or slightly smaller) reduction possible if more were known on SCLC and NSCLC risks from radiation
- New NASA Radiation quality model frames approach to integrate experimental data with track structure descriptions
 - Improved uncertainty analysis of space radiation risks
 - Data on RBE_{max} at saturation point in established model of human cancer is critical experiment leading to largest uncertainty reduction
- Important question remain with regards to radiation tracks and the role of cell killing and target size.
 - These factors most influential on “slope” and position of maximum of “Risk” per particle



Conclusions- continued

- Updates to NASA model 2010 are expected as NSCOR and other data sets are published; as related to refined DDREF and RBE values including tissue specific estimates
- However, the “Standard” model has an inherent uncertainty that likely preclude achieving NASA’s goals for radiation safety on Mars mission
- NSRL program and theoretical/experimental approach to Modular systems biology to develop disease models is long-range approach for NASA program